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Strategies to Improve Long-Term Outcome in Stage IIIB Inflammatory Breast Cancer: Multimodality Treatment Including Dose-Intensive Induction and High-Dose Chemotherapy

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Inflammatory breast cancer (IBC) is a rare clinicopathologic entity with a poor prognosis, lagging far behind any other form of nonmetastatic breast cancer. Since the advent of systemic chemotherapy over 35 years ago, only minimal progress has been made in long-term outcome. Although multiple randomized trials of high-dose chemotherapy and autologous progenitor cell transplantation (ASCT) for the treatment of breast cancer have yielded disappointing results, these data are not necessarily relevant to IBC, a distinct clinical and pathologic entity. Therefore, the optimal multimodality therapy for IBC is not well established, and remains unsatisfactory. We treated 21 women with nonmetastatic IBC with a multimodality strategy including high-dose melphalan (Mel)/etoposide and ASCT. The treatment was overall tolerated with acceptable morbidity, and no post-ASCT 100-day mortality. With a median potential follow-up of approximately 8 years, the estimated progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) at 6 years from on-study date are: 67%, 55%, and 69%, respectively. These results from a small phase II study are among the most promising of mature outcome data for IBC. They strongly suggest, along with results of several already published phase II trials, that ASCT could play a significant role in the first line treatment of IBC.

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INTRODUCTION

Inflammatory breast cancer (IBC) is a rare clinicopathologic entity [1] (1%–2% of all breast carcinoma) with a very poor prognosis. Historically, IBC response to conventional treatment consisting of surgery or radiation therapy alone was short lived, with a time to progression of 12 to 15 months with long-term overall survival (OS) rarely reaching 15%. The mortality rate in IBC after a local recurrence is close to 100% and most patients with local recurrence die with metastatic disease. The advent of successful combination chemotherapy regimens, along with local irradiation of the breast and regional lymphatics has increased the 5-year disease-free survival (DFS) rate to 30% to 35% [2-4], but the long-term survival is still significantly inferior to what is being achieved in other high-risk, nonmetastatic breast cancers (BC) [5]. The most recent SEER data estimates the median survival of women with stage IIIB IBC at 2.9 years versus 6.4 years with other locally advanced BC [6]. The optimal multimodality therapy remains unestablished and current therapy unsatisfactory [7]. Outside of selected tertiary care centers, the prognosis is even poorer, mostly because of the aggressive nature of IBC and of later diagnosis [8].

High-dose chemotherapy followed by autologous progenitor blood cell transplantation (ASCT) has

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been extensively studied in high-risk nonmetastatic BC and is a particularly attractive modality for IBC because of the diffuse and aggressive nature of the disease and its propensity to early micrometastasis. From 14 published randomized trials evaluating ASCT efficacy in high-risk nonmetastatic BC [9-23], has emerged a de facto general consensus that ASCT does not provide a substantial therapeutic advantage for high-risk nonmetastatic BC, although 2 separate meta-analyses of these trials support a modest (13%-15%) improvement in event-free survival (EFS) (but not OS) with ASCT [24,25]. No such assertion of consensus, however, can be made for IBC from these studies because they either specifically excluded subjects with IBC or lacked power for meaningful subset analysis (a total of 30 of 6063 enrolled patients may have had IBC).

The only outcome data on large numbers of IBC patients treated with ASCT originate from the transplant registries of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Blood and Marrow Transplant (EBMT) Solid Tumors Working Party. They are suggestive of a beneficial effect of ASCT, but have not been formally reported. In its 2000 summary report, the CIBMTR reported a 57% 3-year OS for nonmetastatic IBC, data based on 811 women who underwent ASCT between 1991and 1997 (no EFS is available). The EBMT Solid Tumors Working Party briefly reported a median PFS of 57 months on 537 transplanted IBC patients [26]. These data should be interpreted with caution, as they arise from unavoidably heterogeneous populations, both in disease status and specific treatment modality.

Several phase II studies of ASCT in nonmetastatic IBC have been conducted, almost invariably, suggesting a substantial benefit over conventional therapy, but most also report on short follow-up of 2 to 3 years. Here, we report mature data of the National Cancer Institute (NCI)'s experience with ASCT in the treatment of IBC and review the available literature.

METHODS

Patient Population

Between September 1996 and September 2008, 21 patients with nonmetastatic IBC were enrolled onto the NCI study 96-C-0104 to evaluate the role of paclitaxel and cyclophosphamide (TC) followed by high-dose melphalan/etoposide (ME) and ASCT in the treatment of IBC. All patients were required to have a diagnosis of carcinoma of the breast, histologically confirmed by the Laboratory of Pathology of the NCI. The diagnosis of IBC was based on the classical clinical syndrome including erythema and edema with peau d'orange appearance. The presence of dermal lymphatic involvement with tumor cells was not a requirement for diagnosis; however, patients without the typical clinical signs, but with evidence of dermal lymphatic invasion on skin biopsy were also included (2 of the 21 patients).

To be eligible, all patients treated for their disease before enrollment on study (chemotherapy and/or definitive surgery) were required to have not failed this therapy and to have no delay between the prior therapy and therapy on study. Other eligibility requirements included: Karnofsky Performance Status >70%, creatinine clearance >60 mL/min, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <3 times or bilirubin <1.5 times the upper limit of normal, absolute neutrophil count (ANC) >1000/mm^3, platelet count >90,000/mm^3, cardiac ejection fraction >45% at rest, and carbon monoxide diffusing capacity (DLCO) >50% of the predicted value. This study was conducted with the approval of the NCI institutional review board. All patients gave written informed consent.

Treatments

Induction chemotherapy; paclitaxel/cyclophosphamide (TC)

The following TC regimen was given every 4 weeks for 3 to 7 cycles, to achieve maximum clinical response: paclitaxel: 53.3 mg/m^2/day continuous intravenous (i.v.) infusion for 3 consecutive days (total dose over 72 hours: 160 mg/m^2) through a permanent central venous access device, cyclophosphamide: 900 mg/m^2/day i.v. over 1 hour, daily for 3 days (total dose 2700 mg/m^2) and mesna: daily dose of 30% of the cyclophosphamide daily dose. Premedication for paclitaxel, (dexamethasone, cimetidine, and diphenhydramine), standard antiemetics (5-HT3 antagonists) and hydration precyclophosphamide were administered to all patients. granulocyte-colony stimulating factor (G-CSF): 5 μ/kg/day subcutaneously (s.c.) was started on day 5 of each cycle and continued until ANC >1000 cells/mm^3; during cycle 2 (peripheral blood stem cell [PBSC] mobilization), the dose was increased to 5 μ/kg twice daily until the last day of apheresis.

Doxorubicin/cyclophosphamide (AC)

Additionally, all patients received an anthracycline-based regimen, either prior to enrollment on study or as part of the pretransplant induction chemotherapy on study. Patients who had not received prior anthracycline received, following TC chemotherapy, 4 cycles of doxorubicin: 60 mg/m^2 i.v. rapid infusion, and cyclophosphamide: 600 mg/m^2 intravenously on day 1 (AC) every 3 weeks.

Apheresis for PBSC

PBSC were collected and cryo-preserved after the second TC cycle. When the white blood cell count

was between 2000/mm^3 and 5000/mm^3, a peripheral CD34$^+$ count was obtained daily. Once the CD34$^+$ count was >20/μL, daily 15 to 25-liter apheresis began. Apheresis could also be started for WBC >5000/mm^3. The target CD34$^+$ cell dose was 4.0 × 10^6 cells/kg of body weight with a required minimum total of 2.0 × 10^6 CD34$^+$ cells/kg to proceed with high-dose chemotherapy and ASCT.

Thus, prior to ASCT, all patients had received an anthracycline-based regimen and a minimum of 3 cycles of TC. Patients receiving TC in the neoadjuvant setting may have received additional cycles (maximum, 7 cycles) until maximum response.

Preparative regimen; melphalan/etoposide (ME)

Before proceeding with the preparative regimen, a minimum of 21 days since the last cycle of chemotherapy, complete hematologic recovery defined as an ANC of >500/mm^3 and absence of nonhematologic toxicity greater than grade 1 (including a cardiac ejection fraction >45%) were required. ME was given on days −6, −5, and −4: melphalan 53.3 mg/m^2 i.v. over 30 minutes daily for 3 days (160 mg/m^2 total dose) and etoposide 600 mg/m^2 i.v. over 8 hours daily for 3 days (1800 mg/m^2 total dose) starting 1 hour after melphalan infusion completion. PBSC were infused on day 0. G-CSF 5 μ/kg/day started on day 0 after the PBSC infusion and continued until the ANC was ≥1000/mm^3. Herpes simplex virus (HSV) seropositive patients received acyclovir prophylaxis until discharge from the hospital then, following hematopoietic recovery, all patients received pneumocystis jerovecii prophylaxis for 6 months.

Locoregional and Additional Therapy

Locoregional therapy was assessed individually. Surgery (modified radical mastectomy) was performed either prior to entry on study or following TC. All patients received radiation therapy starting 6 weeks after ASCT. Patients usually received 5000 cGy with an additional 1000 cGy chest wall boost. Patients with hormone receptor (HR)-expressing tumors received tamoxifen 20 mg or anastrazole 1 mg daily for 5 years posttransplant starting after completion of radiation therapy. Patients with Her-2 overexpressing tumors did not receive specific antibody therapy.

Disease Evaluation

At entry on study, metastatic disease was excluded in all patients with a computed tomography (CT) scan of chest, abdomen, and pelvis, a bone scan, and a head CT scan or magnetic resonance imaging (MRI). Tumor markers were not routinely obtained. All patients were restaged clinically and radiologically after the first 3 and every 2 subsequent TC cycles. Prior to ASCT, the restaging also included a repeat brain CT scan or MRI. Patients underwent a clinical reevaluation 6 weeks following ASCT, then every 3 months for 2 years, every 6 months for 1 year, and yearly thereafter. Imaging reevaluations were performed at 6 weeks, then 6, 12, 18, and 24 months post-ASCT routinely, then only as clinically indicated. Disease response was evaluated as follows: complete response (CR): disappearance of all clinical and radiologic disease and no new lesion; partial response (PR): >50% disease reduction in existing measurable disease and no new lesion; stable disease (SD): <25% change in existing measurable disease; progressive disease: >25% increase in existing measurable disease or appearance of new lesions.

Patients with PD at any reevaluation or patients with less than PR at the reevaluation immediately before ASCT were considered treatment failures and taken off the study. All toxicities for TC and ME were recorded using the NCI Common Terminology Criteria 2.0 version.

Statistical Methods

The durations of progression-free survival (PFS), EFS, and OS were calculated from the date the patient went on-study, as well as the date of ASCT, until the date of disease progression (PFS), the date of an event defined as either the date of disease progression or death of any cause (EFS), the date of death from any cause (OS), or last follow-up as appropriate. The probabilities of these outcomes as a function of time were determined by the Kaplan-Meier method. The statistical significance of the difference between 2 Kaplan-Meier curves was determined by a 2-tailed log-rank test; all *p*-values are reported without adjustment for multiple comparisons. The median potential follow-up was calculated as the median of the intervals from on-study date as well as transplant date until the date of analysis and provides a reasonable measure of the maturity of the trial.

RESULTS

From September 1996 to September 2008, 21 patients with nonmetastatic IBC were enrolled in the study. Patients characteristics and outcome are summarized in Tables 1 and 2. The mean age at entry on study was 50.3 years (range: 35-67 years) and 11 patients (50%) were postmenopausal. Fifty-two percent and 60% of the tumors were HR positive and Her-2 overexpressed, respectively. Ten patients (48%) had received some form of treatment prior to entry on study (neo-adjuvant chemotherapy and/or definitive surgery). Twelve of 21 patients had disease evaluable for the TC induction chemotherapy: there were 11 (92%) responses (7 CR: 58% and 4 PR: 33%) and 1 SD (9%). There was 1 pathologic CR (9%). The

Table 1. Patients Characteristics

Pts	Age at Entry	ER / PR /Her-2	Post Menop.	Clinical IBC	Dermal TLI	Initial Tumor Size (cm)
1	41	− / − / +	−	+	?	13
2	35	+ / +/ +	−	+	+	10
3	59	− / − / +	−	+	+	2.5
4	60	+ / + / −	+	+	+	12
5	62	+ / − / ?	+	+	?	5
6	41	−/ − / +	−	+	−	no mass
7	39	+ / + / +	−	+	+	no mass
8	46	− / − / ?	−	+	+	12
9	57	− / − / +	+	+	+	no mass
10	68	+ / − / −	+	+	+	3.2
11	54	− / − / +	+	+	+	7
12	43	+ / + / −	−	−	+	4
13	44	+ / + / −	+	−	+	4
14	56	− / − / +	+	+	+	5.5
15	36	− / − / +	−	+	−	7
16	45	+ / − / +	+	+	+	5
17	51	+ / − / +	+	+	+	no mass
18*	60	− / − / −	+	+	?	no mass
19	35	+ / + / −	−	+	+	no mass
20	60	− / − / −	−	+	−	no mass
21	66	+ / − / +	+	+	+	3

ER/PR indicates estrogen/progesterone receptor; TLI, tumor lymphatic invasion; IBC, inflammatory breast cancer.
*Patient presented at diagnosis with bilateral IBC.

only patient with SD after TC reached a PR with the subsequent AC regimen. Therefore, all evaluable patients achieved the minimum required response and 20 of 21 patients proceeded to the high-dose chemotherapy. The only patient not undergoing ASCT died of sepsis after delaying seeking treatment during neutropenia following a TC cycle.

The toxicity of the treatment strategy (TC followed or preceded by AC, followed by high-dose ME and ASCT) is within generally acceptable limits, and was previously reported in a larger cohort of patients [27]. The hematologic toxicity of the TC regimen was noteworthy, but manageable, with brief hospitalization for empiric antibiotic therapy of febrile neutropenia occurring in 55% of the cycles. All 21 patients had adequate PBSC collections. Mortality within 100 days of ASCT was zero. Three of the 8 deaths were not related to disease progression:

Table 2. Patients Outcome

Pts	Prior Therapy+	No. of TC Cycles	Clinical Response to TC	Pathologic Response to TC	Residual Tumor Size at MRM (cm)	Lymph Nodes at MRM (Positive/ Total)	EFS from on Study (Months)	EFS from ASCT (Months)	OS from on Study (Months)
1	+	3	NE	NE	residual foci	0 / 15	142 +	140 +	142 +
2	+	4	NE	NE	residual foci	7 / 28	97 +	94 +	97 +
3	+	3	NE	NE	2.4	12 /12	136 +	133 +	136 +
4	−	4	SD	PR	5	24 /24	84	76	85
5	−	7	CR	PR	residual foci	11 / 11	59	48	59
6	−	5	CR	PR	residual foci	7 / 14	113 +	106 +	113 +
7	−	5	PR	PR	7	6 /14	106 +	96 +	106 +
8	−	5	PR	PR	residual foci	3 / 15	15	8.8	95 +
9	+	4	NE	NE	3.5	16 / 16	24	21	75
10	+	3	NE	NE	6	27 / 28	11	6.9	11
11	−	5	PR	PR	residual foci	2 / 14	98 +	90 +	98 +
12	+	5	NE	NE	4	20 / 20	82 +	76 +	82 +
13	+	5	NE	NE	4	15 / 16	79 +	72 +	79 +
14	−	5	CR	CR	-	0 / 6	68 +	59 +	68 +
15	−	5	CR	PR	residual foci	0 / 11	21	12	22
16	−	5	CR	PR	3 cm	3 / 11	55 +	46 +	55 +
17	−	4	PR	NE	na	na	3.4	na	3.4
18*	+	3	CR	PR	residual foci	0 / 0	14	9.0	33
19	+	3	NE	NE	residual foci	7 / 17	12	9.3	18
20	+	3	NE	NE	6	6 / 12	23	20	25 +
21	−	3	CR	PR	2.1	8/12	9 +	1.4 +	8.6 +

TC indicates paclitaxel/cyclophosphamide; MRM, modified radical mastectomy; NE, not evaluable; CR, complete remission; PR, partial remission; EFS, event-free survival; OS, overall survival; ASCT, autologous progenitor cell transplantation.
*Prior therapy usually consisted of receiving AC and /or definitive surgery prior to entry on study.

a 51-year-old woman, died of sepsis prior to ASCT; a 67-year-old woman died 6 months post-ASCT from progressive multifocal leukoencephalopathy in the absence of BC recurrence (confirmed at autopsy); and a 66-year-old patient died of pneumonia, disease-free, 47 months post-ASCT. Seven patients had a disease recurrence; 3 patients relapsed at 9 months, and 1 each at 12, 20, 21, and 78 months following ASCT. It is noteworthy that not achieving a pathologic CR following TC chemotherapy was not predictive of a shorter EFS; 5 of the 10 patients (50%) achieving a pathologic PR are still clinically free of disease (EFS: 1 patient at 8+ months and 4 patients from 58+ to 123+ months), whereas the patient with a pathologic CR prior to ASCT has a 66+ month EFS.

The median follow-up was 8.4 years from on-study date (n = 21) and 8.3 years from transplant date (n = 20). The probabilities of PFS, EFS, and OS were 67%, 60%, and 75%, respectively, at 3 years and 67%, 55%, and 69%, respectively, at 6 years from the on-study date (Figure 1a). The survival estimates are detailed in the Supplemental Table on-line. No statistically significant difference in any of these 3 outcome measures was seen between HR-positive and HR-negative patients. Statistically significant differences were seen in PFS and EFS (but not in OS) from on-study date between the Her-2 overexpression and nonoverexpression groups with the following 6-year probabilities and corresponding 2-tailed log-rank test results for the comparisons: PFS: 80% versus 50%, $P = .034$; EFS:

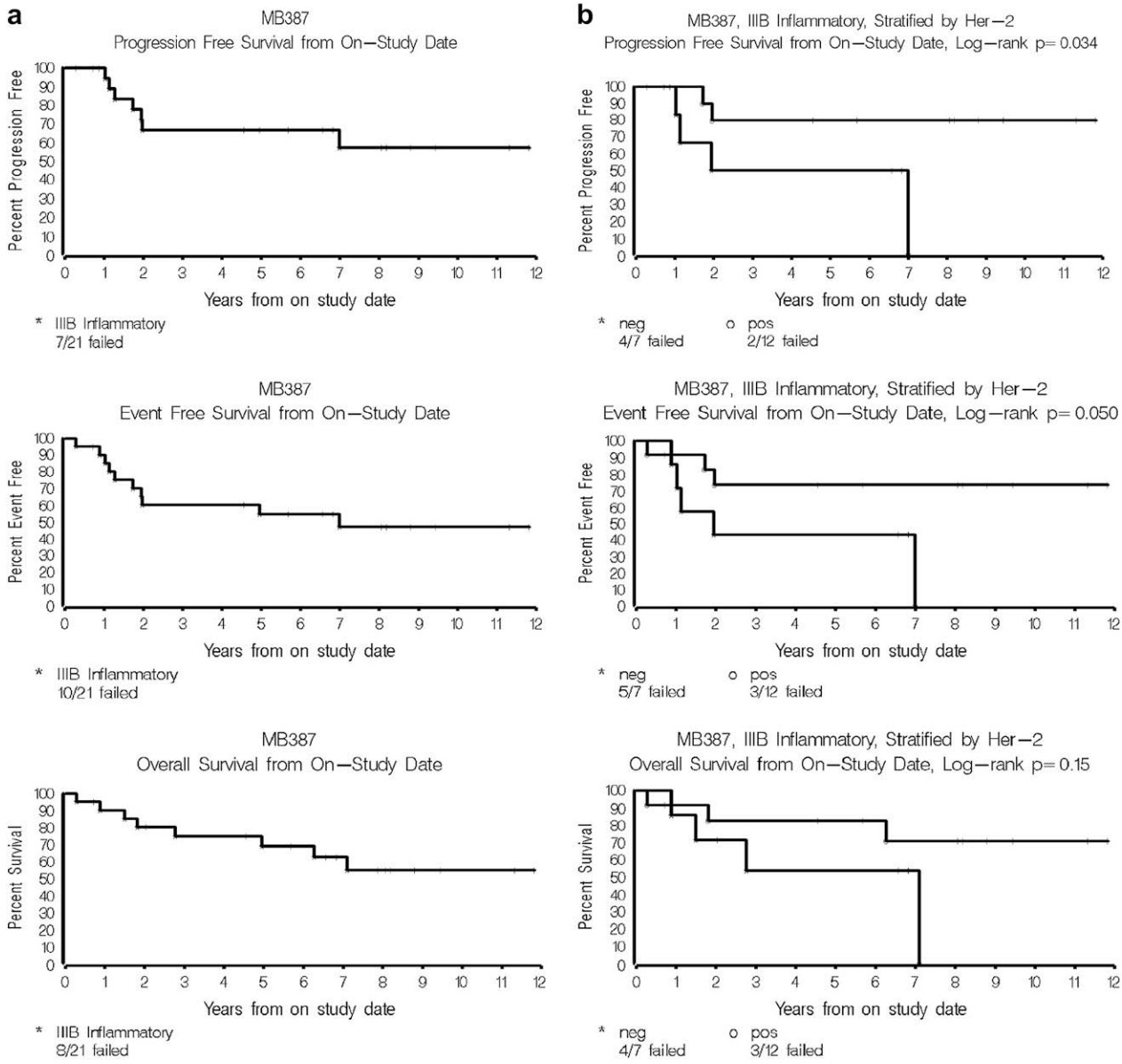

Figure 1. Survival curves (Kaplan-Meyer) for PFS, EFS, and OS from on-study date.(a) All patients; (b) patients stratified by Her-2 status (*P*-values of Log rank test are indicated).

73% versus 43%, $P = .050$; OS: 83% versus 54%, $P = .15$ (Figure 1b, Supplemental Table on-line).

DISCUSSION

Since the addition of systemic chemotherapy to locoregional treatment, now over 30 years ago, and despite some progress in response rate, no substantial progress has been made in the long-term outcome of IBC, either by the addition of taxanes or by varying the drug combinations [4,28]. Newer therapies are providing invaluable insight in to the disease [29], but have yet to demonstrate a decidedly superior therapeutic potential in a disease that lags so far behind other non metastatic BC in long-term survival.

Although high-dose chemotherapy followed by ASCT has not been found to be beneficial in the treatment of high-risk nonmetastatic BC and has been largely abandoned for this indication, no data from randomized clinical trials exist to reach the same conclusion for IBC. Data from 2 transplant registries suggest some efficacy of ASCT in treating IBC, although neither registry has formally reported their results.

Several published phase II studies have found outcome benefit from ASCT in IBC patients [30-36]. Published studies are summarized in Table 3 along with our data. Viens et al. [30] reported on 17 consecutive IBC patients with a median follow-up of 36 months (range: 17-52) with a disease-free survival (DFS) of 58.8% from diagnosis, then subsequently reported a collaborative study in 100 women with nonmetastatic IBC (Pegase 2 trial [34]) with 3-year estimated relapse-free survival (RFS) and OS of 44% and 70%, respectively. Cagnoni et al. [37] reported a cohort of 30 IBC patients with a median follow-up of 2 years, subsequently expanded to 56 patients with longer follow-up [38] with DFS of 65% and OS of 70% at 7 years. Ayash et al. [39] reported on 46 women with IBC with a 30-month DFS of 64%. The 30-month DFS was estimated at 100% for patients in pathologic CR, 70% with microscopic or 38% with gross disease after ASCT. Adkins et al. [31] reported on 47 consecutive IBC patients: at a mean follow-up of 30 months, the 30-month estimated DFS and OS were 57% and 59%, respectively. In the study by Schwartzberg et al. [33], 56 IBC patients were treated: with a median follow-up of 47 months, the 3-year estimated EFS and OS were 53% and 72%. Dazzi et al. [40] investigated the usefulness of a neo-adjuvant high-dose anthracycline containing chemotherapy in 21 patients. Although response rate and outcome were encouraging, there was significant toxicity, cardiac in particular. It noteworthy that, because the recurrence-free interval in IBC is historically considerably shorter than non-IBC, the shorter median follow-up in these studies still suggests an encouraging outcome.

We report here on 21 patients with nonmetastatic IBC following a treatment regimen successfully piloted in our institution, which includes dose-intensive paclitaxel/cyclophosphamide induction [41] then ASCT following high-dose melphalan/etoposide [27]. As previously reported, the HR status does not appear to be of added prognostic value in our series, whereas, unlike what is reported for standard-dose chemotherapy trials, achieving a pathologic CR with standard chemotherapy does not appear to be of prognostic significance in our series, which further argues in favor of an added therapeutic benefit from the high-dose chemotherapy following the determination of disease status pathologically. To our knowledge of the published mature literature on IBC outcome, encompassing mostly standard-dose chemotherapy, these data represent the most favorable outcome in the first line treatment of this disease and significantly contributes to the body of evidence in support of ASCT for IBC, not only by its outcome data but also by its maturity.

In conclusion, a significant body of phase II data has now accumulated and matured, indicating that ASCT may offer a significant benefit in the first-line treatment of nonmetastatic IBC, and in the unfortunate absence of data from randomized trials to confirm or invalidate it, it collectively represents the best

Table 3. Summary of Published Studies of High-Dose Chemotherapy and Stem Cell Transplantation in IBC

Authors	N	Preparative regimen	DFS	OS	Reference
Viens	17	Mi, Cy, M	66% at 3 years	86% at 3 years	[30]
Cagnoni updated series	30 51	CPDD, Cy, BCNU	70% at 2 years 65% at 7 years	87% at 2 years 70% at 7 years	[37] [38]
Ayash	46	CTCb	64% at 30 months	89% at 30 months	[39]
Adkins	47	Various regimens	58% at 4 years	59% at 4 years	[31]
Schwartzberg	56	CTCb	53% at 3 years	72% at 3 years	[33]
Viens	100	Sequential high-dose	44% at 3 years	70% at 3 years	[34]
Arun	24	Cy, Cb	71% at 2 years	73% at 2 years	[32]
Dazzi	21	MI, Thiotepa, Cy	54% at 4 years	63% ay 4 years	[40]
NCI	21	M, Etoposide	67% at 3 years 67% at 6 years	75% at 3 years 75% at 6 years	

Mi indicares Mitoxantrone; Cy, cyclophosphamide; Mel, melphalan; CPDD, cisplatin; CTCb; cyclophosphamide, thiotepa, carboplatin; NCI, National Cancer Institute; DFS, disease-free survival; OS, overall survival.

outcome data for this disease. Our data, therefore, confirm as well as extend available findings; both aspects are of substantial value in the field of ASCT and IBC therapy as it now stands. As none of the newer therapeutic approaches presently under investigation has outcome data yet approaching ASCT results (either in treatment efficacy or data maturity), we believe that substantial collaborative efforts should be devoted to validate these results in a well designed and adequately powered phase III randomized trial.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbmt.2009.04.018.

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